Docket No.: 36731S-000001/US
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Bjarne Bogen et al.

Application No.: 10/786,907 Confirmation No.: 6743

Filed: February 25, 2004 Art Unit: 1643

For: Modified Antibody Examiner: L. A. Bristol

**APPEAL BRIEF**

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on December 1, 2011, and is in furtherance of said Notice of Appeal.

Applicant hereby petitions under the provisions of 37 C.F.R. § 1.136(a) for an extension of time in which to file this Appeal Brief and includes a fee as set forth in 37 C.F.R. § 1.17(a) for such extension of time.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

| | |
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## I. REAL PARTY IN INTEREST

The real party in interest in the present application is Vaccibody AS to which the Medinnova AS had assigned all rights in this invention. The assignment was recorded in the United States Patent and Trademark Office on March 2, 2007, at reel/frame: 019007/0994. The inventors assigned all rights to the invention to Medinnova AS. The assignment was recorded in the United States Patent and Trademark Office on August 17, 2004, at reel/frame: 015693/0408.

## II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

## III. STATUS OF CLAIMS

### *A. Total Number of Claims in Application*

There are 66 claims pending in application.

### *B. Current Status of Claims*

1. Claims canceled: 38-76, 78-82, 95-96, 109-118, 120, 122, 124-130
2. Claims withdrawn from consideration but not canceled: 1-37, 77, 84-87, 93, 94, 97, 101-108
3. Claims pending: 1-37, 77, 83-94, 97-108, 119, 121, and 123
4. Claims allowed: n/a
5. Claims rejected: 83, 88-92, 98-100, 119, 121, and 123

### *C. Claims On Appeal*

The claims on appeal are Claims 83, 88-92, 98-100, 119, 121, and 123.

## IV. STATUS OF AMENDMENTS

All of the amendments have been entered in this application.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

### *A. Nucleic acid*

Claim 83 describes an isolated nucleic acid encoding a monomer unit of a recombinant antibody-based dimeric molecule. The monomer unit contains an antigenic unit, a dimerization motif and a targeting unit. The antibody-based dimeric molecule comprises two of the monomer units connected through the dimerization motif, the dimerization motif comprising an Ig hinge region and a Cγ3 domain of each monomer unit. Claim 83 further provides each Ig hinge region contributes to dimerization via disulfide bridging to the other Ig hinge region and each Cγ3 domain contributes to dimerization via hydrophobic interactions to the other Cγ3 domain. Each of the monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit. The targeting unit and the antigenic unit in the monomer unit are separated by the dimerization motif. The monomer units each lack a CH2 domain.

### *B. Vector and other compositions containing the nucleic acid*

In another aspect, the present invention provides a vector comprising the nucleic acid. In other aspects, the present invention provides a composition comprising a nucleic acid or a vector comprising the nucleic acid in combination with a physiologically acceptable diluent or carrier. In yet other aspects, the present invention provides a kit for preparation of a recombinant antibody-based molecule encoded by the nucleic acid, the kit comprising a nucleic acid. The nucleic acid described is in accordance with Claim 83.

### *C. Structure of the polypeptide encoded by the claimed nucleic acid*

As described above and in Applicants' specification at Paragraph 0011, Claim 83 relates to a nucleic acid molecule that encodes a monomer, *i.e.* a single polypeptide. The structure of the encoded polypeptide can schematically be presented as:

AU – DM – TU

where AU is an antigenic unit, DM is a dimerization motif and TU is a targeting unit for an antigen presenting cell

The dimerization motifs include an Ig hinge region and a Cγ3 domain. As noted at Paragraph 0038, the hinge contributes to the dimerization through the formation of interchain disulfide bridges. In addition, it functions as a flexible spacer between the domains allowing the two scFvs with targeting tasks to bind simultaneously to two target molecules expressed with variable distances (FIG. 2). The Cγ3 domains contribute to the dimerization through hydrophobic interactions.

Finally, the polypeptide encoded by the claimed nucleic acid forms a dimeric molecule, which has the structure:

AU – DM – TU

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AU – DM – TU

where the symbol "|||" indicates the binding between the 2 units; the binding is according to the claim language constituted by 1) disulfide bridging between the Ig hinge regions of the two polypeptides and 2) hydrophobic interactions between the 2 Cγ3 domains of the two polypeptides.

Also, the entire polypeptide lacks a CH2 domain. As set forth in Applicants' specification at Paragraph 0039 the polypeptides lack a CH2 domain and hence all FcR binding sites, and should therefore exclusively be taken up through its target molecules, such as MHC class II in the example used and not by any FcRs, ensuring that a large proportion of the polypeptides will arrive at the intended target cells.

The main claim are mapped to the specification (37 CFR §41.37(c)(v)) as follows:

| Claim | Support in Specification |
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| 83. An isolated nucleic acid encoding a monomer unit of a recombinant antibody-based dimeric molecule, said nucleic acid encoding<br><br>an antigenic unit,<br><br>a dimerization motif and<br>a targeting unit operably connected to encode said monomer unit, and | See Figure 19, Detailed figure of Vaccibody gene construct. The targeting unit is inserted between the BsmI/MfeI and BsiWI restriction enzyme sites (The V cassette of the pLNOH$_2$ vector). The hinge-Cγ3-Fv315 is inserted between the HindIII and BamHI sites into the C cassette of pLNOH2. The hinge and the Cγ3 domain as well as the two scFv's are connected with $(G_4S)_3$ linkers (black boxes). The Cγ3 and the $Fv^{315}$ are connected through a GLSGL linker. The $Fv^{315}$ is inserted between two nonidentical SfiI restriction enzyme sites. The antigenic unit and dimerization motif may be of any origin appropriate. Also, functional fragments of Cγ3 may be employed, or a sequence which is substantially homologous to the Cγ3 sequence or Cγ3 fragments. Figure 19, pp. 10-11, ll. 11-2. |
| wherein said antibody-based dimeric molecule comprises two of said monomer units connected through said dimerization motif,<br><br>said dimerization motif comprising an Ig hinge region and a Cγ3 domain of each monomer unit,<br><br>wherein each Ig hinge region contributes to dimerization via disulfide bridging to the other Ig hinge region and<br><br>each Cγ3 domain contributes to dimerization via hydrophobic interactions to the other Cγ3 domain, and | The crucial dimerization motifs in the Vaccibodies constructed in the examples so far, include hinge regions and Cγ3 domains. The hinge contributes to the dimerization through the formation of interchain disulfide bridges. In addition, it functions as a flexible spacer between the domains allowing the two scFvs with targeting tasks to bind simultaneously to two target molecules expressed with variable distances (FIG. 2). The Cγ3 domains contribute to the dimerization through hydrophobic interactions. These dimerization motifs can be exchanged with other multimerization moieties (e.g. from other Ig isotypes/subclasses). p. 15, ll. 4-11. |
| wherein each of said monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit, | See Figure 1, The structure of the Vaccibody. The two scFvs in white target the Vaccibody to surface molecules on APC. They may be replaced by other targeting molecules, e.g. chemokine receptors. The hinge provides flexibility of the relative orientation of the two NH2-terminal scFvs and disulfide bridges the monomers. The CH3 domains (light grey) act as a spacer between the $NH_2$ and COOH terminal scFvs and participate in the dimerization through hydrophobic interactions. These dimerization motifs may be replaced by other dimerization or multimerization domains. The two scFvs shown in dark grey are the antigenic moiety of the Vaccibody. These scFvs are derived from the M component, thus harboring idiotypic sequences (black). The antigenic scFv may be replaced by any |

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| | polypeptide derived from an antigenic source, conferring vaccine strategies towards any antigen. Figure 1, p. 6, ll. 1-11. |
| wherein said targeting unit and said antigenic unit in the monomer unit are separated by said dimerization motif and | |
| wherein said monomer units each lack a CH2 domain. | The Vaccibodies lack a CH2 domain and hence all FcR binding sites, and should therefore exclusively be taken up through its target molecules, such as MHC class II in the example used and not by any FcRs, ensuring that a large proportion of the vaccine will arrive at the intended target cells. This is in contrast to vaccines that exert their effect through the binding to an FcR on a target cell (Ravetch and Bolland 2001). pp. 15-16, ll. 12-6.<br><br>Other description:<br>See Figure 8, Construction of the two hinge-Cy3 variants derived from hIgG3 by PCR. The templates were from pUC19 containing modified hIgG3 constant regions were the h4 exon were connected to the CH3 domain (A) or the h1 exon were connected to the h4 exon further connected to the CH3 domain (B) (Olafsen T et al, 1998). The primers inserted HindIII (5') and SfiI (3') restriction enzyme sites. The hinge and CH3 domain are connected by a triplicate of the amino acids GlyGlyGlySerSer. Figure 8, p. 8, ll. 8-14.<br><br>See Figure 9, Construction of the hinge-Cy3 segments derived from mIgG2b. The hinge and the CH3 genes were amplified from a pUC18 vector containing the constant region of mIgG2b by PCR with two primers encoding a HindIII (5') and a SfiI (3') restriction enzyme site. The two PCR fragments were joined by PCR SOEing. In this reaction, the hinge and CH3 domain were connected by a triplication of the amino acids Gly-Gly-Gly-Ser-Ser. Figure 9, p. 8, ll. 15-20.<br><br>See Figure 10, Construction of the scFv derived from the myeloma protein M315. The cDNA that functioned as a template in the PCR reactions were derived from mRNA extracted from MOPC315.4 cells. The V regions were joined by PCR SOEing resulting in a scFv. In this reaction, the V regions were connected by a triplicate of GlyGlyGlyGlySer. Furthermore, the gene fragments encoding the complete scFv were flanked by SfiI and SalI restriction enzyme sites. Figure 10, p. 9, ll. 1-6.<br>See Figure 11, Joining of the hinge-Cy3 segments and the M315 scFv by PCR SOEing. This reaction introduced the SfiI site 5' of the |

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| | antigenic scFv encoding region. Figure 11, p. 9, ll. 7-9.<br><br>See Figure 12, Subcloning of the hinge-Cγ3-M315 scFv into pUC19. Three different dimerization motifs were included, derived from mIgG2b or IgG3. In all cases, they consisted of hinge followed by a triplicate of GlyGlyGlySerSer and CH3. Two different hinges were derived from hIgG3, one consisting of h1 linked to h4, and one consisting of h4, only. Figure 12, p. 9, ll. 10-14.<br><br>See Figure 13, Removal of two inconvenient BamHI restriction enzyme sites within the gene fragment encoding the antigenic scFv by QuickChange PCR. Figure 13, p. 9, ll. 15-16.<br><br>See Figure 14, Introduction of stop codon, a SfiI and a BamHI restriction enzyme site downstream of the coding region by QuickChange PCR. Figure 14, p. 9, ll. 17-18.<br><br>See Figure 15, Subcloning into the C cassette of the expression vector pLNOH$_2$ on HindIII-BamHI. Figure 15, p. 10, ll. 1-2.<br><br>See Figure 16, Cloning of the V regions specific for NIP and MHCII. The V regions were amplified and joined by PCR soeing resulting in scFvs. The linker connecting the V regions consists of a triplicate of GlyGlyGlyGlySer. The gene fragments encoding the complete scFvs are flanked by BsmI/MunI and BsiWI sites. Linkers and restriction sites were introduced in the PCR reactions. Figure 16, p. 10, ll. 3-7.<br><br>See Figure 17, Subcloning into the expression vector pLNOH2 on BsmI/MunI and BsiWI. Figure 17, p. 10, ll. 8-9.<br><br>See Figure 18, The final Vaccibody construct. Figure 18, p. 10, l. 10.<br><br>The present invention relates to a recombinant human antibody-based molecule, called Vaccibodies, comprising dimers of a monomeric unit that consist of a single chain fragment variable (scFv) of immunoglobulins (Ig) with specificity for surface molecules on Ag presenting cells (APC), connected through a hinge region and a Cγ3 domain to a scFv in the COOH-terminal end, the latter being derived from a myeloma protein (FIG. 1), although any origin is possible due to the cassette cloning system of the expression vector. The hinge |

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| | region and the Cγ3 domains (carboxyterminal C domain of Ig) contribute to dimerization of the Vaccibody through disulfide bridges in the hinge and strong hydrophobic interactions between the two Cγ3 domains. Hence, the dimeric product will include two preferably identical scFvs with binding specificity for the same surface molecules on APC (FIG. 2), enabling bivalent binding. pp. 13-14, ll. 14-4.<br><br>The crucial dimerization motifs in the Vaccibodies constructed in the examples so far, include hinge regions and Cγ3 domains. The hinge contributes to the dimerization through the formation of interchain disulfide bridges. In addition, it functions as a flexible spacer between the domains allowing the two scFvs with targeting tasks to bind simultaneously to two target molecules expressed with variable distances (FIG. 2). The Cγ3 domains contribute to the dimerization through hydrophobic interactions. These dimerization motifs can be exchanged with other multimerization moieties (e.g. from other Ig isotypes/subclasses). p. 15, ll. 4-11.<br><br>The C-terminal scFv derived from the monoclonal Ig produced by myeloma or lymphoma cells, also called the myeloma/lymphoma M component, can be genetically exchanged with other scFvs or any antigen because the vector has been constructed with a Sfi I restriction site (FIG. 8)…The Vaccibodies lack a CH2 domain and hence all FcR binding sites, and should therefore exclusively be taken up through its target molecules, such as MHC class II in the example used and not by any FcRs, ensuring that a large proportion of the vaccine will arrive at the intended target cells. This is in contrast to vaccines that exert their effect through the binding to an FcR on a target cell (Ravetch and Bolland 2001). pp. 15-16, ll. 12-6. |

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 83, 88-92, 98-100, 119, 121, and 123 stand rejected under 35 U.S.C. §103(a) as unpatentable over Herman (U.S. Pub. No. 2005/0069549, published March 31, 2005, filed January 14, 2003; cited in the PTO 892 form of 11/7/2006 (herein "*Herman*") in view of Slavin-Chiorini et al. (Int. J. Can. 53:97-103(1993)) (herein "*Slavin*").

## VII. ARGUMENT

### *A. Contrary to the Examiner's stated position, the combined references – Herman and Slavin - do not contain all of the claim features arranged as presented in the claims*

A *prima facie* case of obviousness is not made out because the references when combined do not contain all of the limitations of the rejected claims. Instead, the claims are reached only through the impermissible use of hindsight reconstruction. Reversal is requested on the basis of the following discussion.

#### 1. Herman discloses an antibody-type molecule, but does not teach a nucleic acid encoding a monomer with a targeting unit and an antigenic unit separated by a dimerization motif

To support the obviousness rejection, the primary reference is alleged to contain all of the claim elements except for the proviso that the monomer units lack a CH2 domain. But the disclosure of *Herman* is deficient in lacking other features of the claims; this argument against the rejection has been given insufficient weight.

In the present case, the primary reference *Herman* would, if the obviousness rejection is correct, need to include ALL technical features of the claimed invention except for the modification(s) obtained from a secondary reference. In order for an obviousness rejection over *Herman* in view of *Slavin* to be correct, *Herman* would have to disclose at least one embodiment of the "multi-specific ligands" taught therein, where one single polypeptide exhibits the structural organisation: antigenic unit – dimerization motif – targeting unit, as recited in the claims where the targeting unit is for an antigen presenting cell. Further, the dimerization motif would have to include an Ig hinge region and a Cγ3 domain. This disclosure is missing from Herman.

For example, consider the claim limitation that the "monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit … separated by [a] dimerization motif," and further wherein the "dimerization motif compris[es] an Ig hinge region and a Cγ3 domain of each monomer unit." This structure is not disclosed in *Herman*, as demonstrated in the following passages that speak of an antigen presenting cell (APC):

1. §0072: This paragraph lists in tabular form a number of putative targets for multifunctional ligands, and some of these are targets for antigen-presenting cells (e.g. dendritic cell markers). However, the paragraph and table do not suggest that the 2 different ligands are part of the same polypeptide and are separated by an Ig hinge region and a Cγ3 domain.

2. §0137: Here it is suggested that the "first moiety" may comprise two different target ligands – it is in particular suggested that one ligand can bind an MHC peptide complex and the other can bind a ligand on an APC. Again, the paragraph does not disclose that the 2 different ligands are part of the same polypeptide and are separated by an Ig hinge region and a Cγ3 domain.

3. §0143: In this paragraph, it is mentioned in a parenthesis that one of the at least 2 ligand binding moieties may bind to an antigen presenting cell. However, the location of this moiety relative to the other ligand binding moiety is not provided (in the paragraph, it is indicated that both moieties are preferably antibodies) meaning that the paragraph i.a. describes a construct having a structure where the two moieties are located in separate polypeptides. No description is provided of a construct where one moiety is present in the same polypeptide and separated by a Cγ3 domain and an Ig hinge region.

4. §0148: This paragraph in essence teaches the same as §0143: Again, there is no mentioning that the 2 different ligand binding moieties are part of the same polypeptide.

5. §0171: In this paragraph, it is indicated that a "first portion" of the multi-specific ligand is "...fused, conjugated or otherwise linked directly or indirectly to an immunizing moiety..." which may be an antibody component that binds to an APC. Again, nothing in this paragraph indicated that the "first portion" and the "immunizing moiety" are separated by an Ig hinge region and a Cγ3 domain in the same polypeptide.

6. §0343: This paragraph (which uses both the term "antigen presenting cell and "APC") mentions that one of the ligand binding moieties may bind to a specific MHC peptide complex and thereby targets the heterofunctional ligand to an APC. Again, there is no teaching that the APC and the targeting moiety and the other moiety are part of the same polypeptide and are separated by a dimerization motif as defined in the present claims.

It is not sufficient for a finding of obviousness that *Herman* teach the presence of certain generic elements (CH3 domains, Ig hinge regions, CH2 domains, targeting units for antigen presenting cells) in the multispecific ligands. To properly support a rejection for obviousness it would be necessary for *Herman* to teach the same overall structural organization of a polypeptide as presently claimed. So, *Herman* is deficient for not disclosing a nucleic acid coding for a polypeptide having the structure antigenic unit – dimerization motif – targeting unit, where the dimerization motif includes an Ig hinge region and a Cγ3 domain and where the targeting unit is for an antigen presenting cell.

**2. The secondary reference *Slavin* does not make up for the deficiencies of the primary reference *Herman***

The Examiner alleges a *prima facie* case of obviousness by combining the teachings of *Herman* with the teachings of *Slavin*. The claims of the present invention recite an isolated nucleic acid encoding a monomer unit of a homodimeric molecule consisting of an antigenic unit (AU), a dimerization motif (DM) and a targeting unit (TU). The DM consists of an Ig hinge region and a

Cγ3 region. *Herman* teaches an antibody-type molecule, but does not specifically teach a nucleic acid encoding a monomer with a TU and an AU separated by a DM. In the claimed invention, the DM does not include a CH2 domain. *Slavin* discloses mouse antibodies lacking a CH2 domain. The rejection is then based on combining Herman and *Slavin* for the latter's "teaching" of removing a CH2 domain.

It is axiomatic that there can be no rejection for obviousness if the references when combined do not contain all of the features of the rejected claims. Combining the references in this way ignores the other deficiencies of the primary reference. As a result of those deficiencies of the primary reference, the combined references do not contain all of the claim elements, arranged as they are in the claims.

Any conclusion to the contrary is based on impermissible hindsight, using the description of the invention as a roadmap to guide reconstruction of the claims from the references. Applicants request reversal of the rejection on the grounds that the references, even when combined, still do not contain all of the claim elements arranged as in the claims.

***B. Even if all the elements were to be found in the cited references, the skilled artisan would not have combined the references, for the reasons of record.***

**1. The two references present incompatible goals with respect to the question of serum half-lives**

Despite the deficiencies of *Herman*, the Examiner concludes that the claimed invention is unpatentable because it would have obvious to import *Slavin's* teaching of no CH2 domain into the disclosure of Herman. The Examiner's position is that the person of skill would have been motivated to so combine the references. But this position is held against a preponderance of evidence supporting the opposite conclusion. As noted above, the combined references still do not contain all of the elements arranged as they are in the rejected claims. And as detailed in the following, the references teach away from their combination.

The main argument here, which has not been refuted by the Examiner, is based on the following two facts: First, *Herman* discusses the possibility only of increasing serum half-life (=decreasing clearance) of the multi-specific ligands. There is no mentioning in *Herman* that it would be of interest, let alone desirable, to decrease half-life (=increase clearance). One can

conclude that *Herman* only aims at maintaining or increasing serum half-life. This fits perfectly with the fact that *Herman* relates to the provision of therapeutic molecules, see paragraphs 0002 - 0005 in *Herman*.

Second, *Slavin* explicitly shows that removal of the CH2 domain in a murine monoclonal antibody decreases the serum half-life (=increases clearance) of the antibody. *Slavin* indicates that this is a desirable feature for diagnostic applications where antibodies labelled with radionuclides are used.

In the Amendment of April 2011, Applicants discussed the incompatible teaching of *Slavin* and *Herman,* noting that the Examiner appreciated the premise of the argument, *i.e.* that the two references present incompatible goals with respect to the question of serum half-lives. Attention is drawn to pages 13-17 of the April 2011 Amendment, including Applicants' summary of the argument:

> Simply put, it is not predictable that an immunotherapy based on the targeted ligand provided by *Herman* would actually benefit by making a CH2-deprived antibody, as per [*Slavin*].

Motivation to combine the references is thus missing, except as found in Applicants' own specification.

**2. The low serum half-life in *Slavin* teaches against the use of antibodies that lack a CH2 domain as a modification of *Herman's* constructs**

*Slavin* teaches that removal of a CH2 domain from a monoclonal murine antibody has the consequence that the specific antibody has a faster clearance rate (=lower serum half-life) than the corresponding unmodified monoclonal antibody. Further, the advantage for certain "clinical protocols," as taught in *Slavin*, appear to be for diagnostic clinical protocols, since nothing else is mentioned, and since the diagnostics discussed in *Slavin* clearly are clinical. The rejection has therefore not reconciled the noted incompatibility of Herman and *Slavin.*

It is also underscored in *Slavin* that further testing is necessary and that other doubts as to the usefulness of the CH2 free antibodies are expressed. *Slavin's* molecule is a murine antibody analogue used in diagnosis – the reference explicitly teaches that it may be (but that it is not certain) that removal of the CH2 domain in such an antibody will generally decrease serum half-life. Here are some of *Slavin's* teachings in this regard:

> Page 102, right-hand column, lines 9-12 (studies of metabolic uptake planned when using other radionuclides); lines 24-28 (the CH2-domain free constructs differ in their chain assembly and comparative studies are necessary); and lines 31-33 (further clinical testing required because the CH2-free antibody exhibits reduced tumour binding).

For a skilled person to be motivated to modify *Herman* by using the approach taken in *Slavin*, he would have to have at least some hint or suggestion from either *Herman* or *Slavin* that *Herman*'s constructs (which are not murine monoclonal antibodies) could somehow benefit from removal of the CH2 domain. But this suggestion is missing from the art.

### *C. Expert opinion on the question of combinability of the references supports Applicants' position*

Applicants provided further evidence of non-obviousness, which they urge has been given insufficient weight. A declaration by E. Sally Ward, Ph.D. accompanied the 10/26/2010 reply to the Examiner's 6/1/10 Final Office Action. Dr. Ward holds a Ph.D. in Biochemistry and Molecular Biology from the University of Cambridge, England, and is currently a professor (with an endowed title) of Molecular Immunology at the University of Texas Southwestern Medical Center in Dallas, Texas. She had performed research concerning molecular immunology for about 20 years at the time of the declaration, and has an impressive record of publishing immunology articles in peer-reviewed journals. Upon reviewing Applicants' claims and the prior art references, Dr. Ward declared:

> It is my position that a person of ordinary skill in the art would not combine and modify the Herman document in view of the Slavin-Chiorini document because Herman refers to prolonged serum half-life as desirable, and consequently a skilled artisan would not turn to Slavin-Chiorini in order to modify the Herman disclosure to decrease the half-life of the multispecific ligand.

Like Dr. Ward, Applicants submit that, since *Herman* deals with immunotherapy where a prolonged serum half-life is desirable, and since *Slavin* relates to clinical diagnosis with a radioisotope where a long serum half-life is not desirable, the two references are antagonistic and so would not be combined by a person of ordinary skill in the art.

Against this, the Examiner appeared to argue that "...if clearance rate is an inventive feature of the claimed antibody structure, none of the instant claims even contain such language..." But this is beside the point: Applicants' argumentation does not relate to the clearance rate of the claimed constructs, but rather to the apparent incompatibility of the *Herman* and *Slavin* references for the purposes of establishing a *prima facie* case of obviousness. *Herman* expresses that increased half-life of a multi-specific receptor is desirable and *Slavin* reports decreased half-life when removing the CH2 domain of a murine antibody. The Examiner has not established how and why it would appear obvious to the skilled person, under these circumstances, to combine *Herman* with *Slavin*, even in a situation where *Herman* would actually disclose a molecule having the above-referenced structure AU – DM – TU (which it does not disclose).

For the aforementioned reasons, the Examiner's *prima facie* showing of obviousness has been rebutted by a preponderance of evidence. Because independent claim 83 is for that reason not obvious from the cited combination of art, each of the rejected dependent claims is patentable for the same reasons.

Accordingly, Applicants respectfully request withdrawal of the rejections and allowance of the claims.

## VIII. CONCLUSION

In view of the above presented discussion, the Applicants believe that the pending claims are patentably distinguishable over the art cited by the Examiner. Accordingly, the Applicants respectfully request that this Board reverse the rejection of Claims

## IX. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include the amendments filed by Applicant on April 14, 2011.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 08-0750, under Order No. 36731S-000001/US from which the undersigned is authorized to draw.

Dated: February 28, 2012

Respectfully submitted,

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## APPENDIX A

This is a complete and current listing of the claims.

1. (withdrawn) A method of treating multiple myeloma or lymphoma in a patient, the method comprising administering to the patient, a recombinant antibody-based molecule comprising two targeting units and two antigenic units connected through a dimerization motif, or a nucleic acid encoding said recombinant antibody-based molecule.

2. (withdrawn) The method of claim 1, wherein administering the nucleic acid comprises delivering the nucleic acid by electroporation.

3. (withdrawn) The method of claim 1, wherein said targeting unit(s) is/are a single chain fragment variable of Ig (scFv).

4. (withdrawn) The method of claim 3, wherein said scFv is anti-HLA, anti-CD14, anti-CD40, or anti-toll-like receptor.

5. (withdrawn) The method of claim 4, wherein said anti-HLA is anti-HLA-DP.

6. (withdrawn) The method of claim 4, wherein said anti-toll-like receptor is anti-toll-like receptor 2.

7. (withdrawn) The method of claim 1, wherein at least one targeting unit is a ligand.

8. (withdrawn) The method of claim 7, wherein said ligand is soluble CD40 ligand or a chemokine.

9. (withdrawn) The method of claim 7, wherein said ligand is a chemokine.

10. (withdrawn) The method of claim 9, wherein said chemokine is RANTES or MIP-1α.

11. (withdrawn) The method of claim 9, wherein said chemokine is MIP-1α.

12. (withdrawn) The method of claim 1, wherein at least one targeting unit is a bacterial antigen.

13. (withdrawn – previously presented) The method of claim 12, wherein the bacterial antigen is a flagellin.

14. (withdrawn) The method of claim 1, wherein the targeting units have the ability to target antigen presenting cells (APC).

15. (withdrawn – previously presented) The method of claim 1, wherein the targeting units have the ability to target HLA, CD14, CD40, a toll-like receptor, or a chemokine receptor.

16. (withdrawn) The method of claim 15, wherein said HLA is HLA-DP

17. (withdrawn – previously presented) The method of claim 1, wherein the targeting units have the ability to target a chemokine receptor.

18. (withdrawn) The method of claim 1, wherein the antigenic unit(s) is/are an antigenic scFv.

19. (withdrawn) The method of claim 18, wherein the antigenic scFv is derived from a monoclonal Ig produced by myeloma or lymphoma.

20. (withdrawn) The method of claim 18, wherein the antigenic unit(s) is/are a telomerase, or a functional part thereof.

21. (withdrawn) The method of claim 20, wherein said telomerase is hTERT.

22. (withdrawn) The method of claim 1, wherein the antigenic unit(s) is/are derived from a bacterium.

23. (withdrawn) The method of claim 22, wherein the bacterium derived antigenic unit(s) is/are a tuberculosis antigen.

24. (withdrawn) The method of claim 1, wherein the antigenic unit(s) is/are derived from a virus.

25. (withdrawn) The method of claim 24, wherein the virus derived antigenic unit(s) is/are derived from HIV.

26. (withdrawn) The method of claim 25, wherein the HIV derived antigenic unit(s) is/are derived from gp120.

27. (withdrawn) The method of claim 1, wherein the dimerization motif comprises a hinge region and an immunoglobulin domain.

28. (withdrawn) The method of claim 27, wherein the hinge region is Ig derived.

29. (withdrawn) The method of claim 27, wherein the hinge region has the ability to form one or several covalent bonds.

30. (withdrawn) The method of claim 29, wherein the covalent bond is a disulphide bridge.

31. (withdrawn) The method of claim 27, wherein the immunoglobulin domain is a carboxyterminal C domain, or a sequence that is substantially homologous to said C domain.

32. (withdrawn) The method of claim 31, wherein the carboxyterminal C domain is derived from IgG.

33. (withdrawn) The method of claim 27, wherein the immunoglobulin domain has the ability to homodimerize.

34. (withdrawn) The method of claim 33, wherein said immunoglobulin domain has the ability to homodimerize via noncovalent interactions.

35. (withdrawn) The method of claim 34, wherein said noncovalent interactions are hydrophobic interactions.

36. (withdrawn) The method of claim 1, comprising administering the nucleic acid to the patient to induce production of the recombinant antibody-based molecule.

37. (withdrawn) The method of claim 1, comprising administering a vector comprising the nucleic acid.

38.-76. (cancelled)

77. (withdrawn) A method of preparing a recombinant antibody-based molecule comprising:

a. transfecting the vector of claim 73 into a cell population;

b. culturing the cell population;

c. collecting recombinant protein expressed from the cell population; and

d. purifying the expressed protein.

78-82. (cancelled)

83. (previously presented) An isolated nucleic acid encoding a monomer unit of a recombinant antibody-based dimeric molecule, said nucleic acid encoding an antigenic unit, a dimerization motif and a targeting unit operably connected to encode said monomer unit, and wherein said antibody-based dimeric molecule comprises two of said monomer units connected through said dimerization motif, said dimerization motif comprising an Ig hinge region and a Cγ3 domain of each monomer unit, wherein each Ig hinge region contributes to dimerization via disulfide bridging to the other Ig hinge region and each Cγ3 domain contributes to dimerization via hydrophobic interactions to the other Cγ3 domain, and wherein each of said monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit, wherein said targeting unit and said antigenic unit in the monomer unit are separated by said dimerization motif and wherein said monomer units each lack a CH2 domain.

84. (previously presented) The nucleic acid of claim 83, wherein at least one of said targeting units is a single chain fragment variable of Ig (scFv).

85. (previously presented) The nucleic acid of claim 84, wherein said scFv is anti-HLA, anti-CD14, anti-CD40, or anti-toll-like receptor.

86. (previously presented) The nucleic acid of claim 85, wherein said anti-HLA is anti-HLA-DP.

87. (previously presented) The nucleic acid of claim 85, wherein said anti-toll-like receptor is anti-toll-like receptor 2.

88. (previously presented) The isolated nucleic acid of claim 83, wherein at least one of said targeting unit is a ligand.

89. (previously presented) The isolated nucleic acid of claim 88, wherein said ligand is soluble CD40 ligand or a chemokine.

90. (previously presented) The isolated nucleic acid of claim 88, wherein said ligand is a chemokine.

91. (previously presented) The isolated nucleic acid of claim 90, wherein said chemokine is RANTES or Macrophage Inflammatory Protein 1 alpha.

92. (previously presented) The isolated nucleic acid of claim 90, wherein said chemokine is MIP-1α.

93. (previously presented) The nucleic acid of claim 83, wherein at least one of said targeting unit is a bacterial antigen.

94. (previously presented) The nucleic acid of claim 93, wherein said bacterial antigen is a flagellin.

95.-96. (cancelled)

97. (withdrawn-previously presented) The nucleic acid of claim 83, wherein said targeting units have the ability to target CD14, CD40, a toll-like receptor, or HLA or HLA-DP.

98. (previously presented) The isolated nucleic acid of claim 83, wherein said targeting unit have the ability to target a chemokine receptor.

99. (previously presented) The isolated nucleic acid of claim 83, wherein at least one of said antigenic unit is an antigenic scFv.

100. (previously presented) The isolated nucleic acid of claim 99, wherein said antigenic scFv has VL and VH chains from a monoclonal Ig produced by myeloma or lymphoma.

101. (withdrawn) The nucleic acid of claim 83, wherein at least one of said antigenic unit is a telomerase or a functional part thereof.

102. (withdrawn) The nucleic acid of claim 101, wherein said telomerase is hTERT.

103. (withdrawn) The nucleic acid of claim 83, wherein at least one of said antigenic units is derived from an infectious agent.

104. (withdrawn) The nucleic acid of any one of claims 83 or 103, wherein at least one of said antigenic unit is derived from a bacterium.

105. (previously presented) The nucleic acid of claim 104, wherein said bacterium-derived antigenic unit is/are a tuberculosis antigen.

106. (previously presented) The nucleic acid of any one of claims 83 or 103, wherein at least one of said antigenic unit is derived from a virus.

107. (previously presented) The nucleic acid of claim 106, wherein said virus-derived antigenic unit is derived from HIV.

108. (previously presented) The nucleic acid of claim 107, wherein said HIV-derived antigenic unit is derived from gp120.

109.-118. (cancelled)

119. (previously presented) A vector comprising the nucleic acid according to claim 83.

120. (cancelled)

121. (previously presented) A composition comprising a nucleic acid according to claim 83 or a vector comprising the nucleic acid according to claim 83, in combination with a physiologically acceptable diluent or carrier.

122. (cancelled) A composition comprising a cell of the cell line according to claim 120, in combination with a physiologically acceptable diluent or carrier.

123. (previously presented) A kit for preparation of a recombinant antibody-based molecule encoded by the nucleic acid according to claim 83, the kit comprising a nucleic acid according to claim 83.

124.-130. (cancelled)

## APPENDIX B

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the examiner is being submitted.

## APPENDIX C

No related proceedings are referenced in II. above, hence copies of decisions in related proceedings are not provided.

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